

Part A
Dendritic Cell Biology

1

Introduction to Some of the Issues and Mysteries Considered in this Book on Dendritic Cells

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The authors, under the leadership of Manfred Lutz, Nikolaus Romani and Alexander Steinkasserer, are to be congratulated for assembling this timely volume on dendritic cells. This book will help all of us to keep up! The special position of dendritic cells in the immune system can be summarized in some general terms. Lymphocytes have exquisite mechanisms for recognizing an infinite array of self and foreign antigens, but they require dendritic cells for many critical functions. Dendritic cells use a specialized endocytic system to capture antigens for processing and display to lymphocytes. Dendritic cells respond to a plethora of stimuli, not only pathogen components but also endogenous ligands including cytokines. While presenting self and foreign antigens, dendritic cells exhibit migratory, homing and lymphocyte binding properties that allow clonal selection to take place. Following clonal selection, dendritic cells influence a key decision, whether lymphocytes are to be tolerized or immunized, and for the latter, dendritic cells control the quality of the immune response through the regulated expression of many co-stimulatory molecules. The purpose of this introduction is to briefly summarize what lies ahead in the chapters of the book, and to do this by restating some of the issues and mysteries that they will consider.

1.1

Dendritic Cells as a Distinct Hematopoietic Lineage

1.1.1

Chapters 1–16, the Life History of Dendritic Cells

The cytokine flt-3L is currently the most effective and selective way to expand the output of many types of dendritic cells, and dendritic cell progenitors can be enriched by their expression of flt-3 [1]. The dendritic cells enter the blood and tissues in precursor and immature forms where they act as sentinels, poised to capture antigens and to respond to an array of environmental cues. An important position for dendritic cells is at mucosal surfaces, where self antigens [2] and microbial

products [3–5] are captured. The information obtained by dendritic cells – both antigens and other stimuli for dendritic cell maturation – is then conveyed to T cells and other kinds of lymphocytes, primarily in lymphoid tissues where dendritic cells encounter innate (NK, NKT) and adaptive (B, T) lymphocytes. At this point, the life span of dendritic cells is limited [6], and the cells do not leave the lymphoid organ because they are not found in efferent lymph [7]. However, there is no doubt that dendritic cells can additionally accumulate in peripheral tissues, for example at sites of delayed type hypersensitivity, and even help to organize lymphoid tissue-like structures in chronic inflammatory disease [8].

1.1.2

Questions Concerning the Dendritic Cell Lineage

As one reads chapters 1–16, many current unknowns will surface. Are there any functional differences between dendritic cells when they arise from lymphoid as opposed to myeloid progenitors? Are the immature dendritic cell progeny that are expanded by flt-3L only committed to become dendritic cells, or can they still “transdifferentiate” to become other types of phagocytes or lymphocytes? What transcription factors control dendritic cell development including distinct subsets? What is the origin of dendritic cells in lymphoid tissues in the steady state? Can some dendritic cells in lymphoid tissues originate directly from the myeloid and plasmacytoid dendritic cell populations in the blood, or do most dendritic cells (also monocytes and subsets of monocytes) first patrol peripheral tissues before moving to the lymphoid organs? What factors are responsible for the entry of dendritic cells from tissues into the afferent lymph in the steady state? This flux is postulated to allow dendritic cells to bring samples of self tissues and environmental proteins to the lymph nodes for purposes of tolerance. What is the *raison d’être* for subsets of dendritic cells? Are they programmed to carry out distinct innate responses by expressing distinct receptors for antigen uptake, toll ligands, and cytokines? If antigens are successfully processed, are all dendritic cell subsets capable of mediating similar forms of tolerance and immunity, depending upon their maturation state? These topics are pertinent to the understanding of the dendritic cell lineage and the control of many aspects of immune function.

1.2

Control of Lymphocyte Responses by Dendritic Cells

1.2.1

Chapters 17–30, Initiation of Immunity

The classical emphasis in dendritic cell biology has been to understand the initiation of T-cell immunity. This remains a focus of chapters 17–30, but attention is also given to more recently appreciated roles of dendritic cells in stimulating other types of lymphocytes and controlling antigen-specific tolerance. There are several

sets of requisite features that dendritic cells express. These include (i) specialized receptors for antigen uptake and efficient processing pathways, including the mysterious cross presentation pathway, whereby non-replicating antigens are processed for presentation on MHC class I and now on other molecules like CD1 [9, 10]; (ii) the production of many membrane co-stimulators (from the B7, TNF and Notch families) as well as cytokines and chemokines; (iii) a group of migratory, homing and lymphocyte binding functions that allow dendritic cells to survey the periphery and move to lymphoid tissues; and (iv) the presence of distinct subsets that can carry out different forms of innate and adaptive resistance. I would like to consider some issues with regard to the first two topics, which are considered at many points in this volume.

1.2.2

Questions Concerning Antigen Uptake, Processing and Presentation

Although dendritic cells have many potential receptors for adsorptive endocytosis, what are the natural ligands for many of these such as DEC-205/CD205, langerin/CD207, and a host of other lectins? Interestingly, antibodies to these receptors can be engineered to express defined antigens, and this would seem to be an important new way to analyze receptor and dendritic cell function *in vivo* [11, 12]. Do these receptors function exclusively to enhance antigen capture, or are they additionally specialized to navigate special processing pathways within the cell and/or to couple with other signaling receptors such as toll like receptors? Might the presentation of “exogenous” antigens on MHC class I best be figured out in dendritic cells, which are so efficient at this pathway *in vivo* following capture of dying cells, immune complexes, and ligands for DEC-205? What underlies the distinct regulation of antigen presentation in dendritic cells, which seems different in different sites? For example, dendritic cells that are derived from bone marrow precursors in culture, as well as Langerhans cells, can markedly increase the efficiency of antigen processing and MHC peptide complex formation during dendritic cell maturation [13–15]. Nonetheless, some steady state dendritic cells in peripheral lymphoid organs are continuously able to form at least some MHC peptide complexes for purposes of immune tolerance [11, 12]. What is the potential role of dendritic cells in direct antigen presentation to B cells, where native antigens are to be recognized [16]? How are dendritic cells recognized by NK lymphocytes [17–20]?

1.2.3

Questions Concerning Dendritic Cell Maturation

Maturation has been an important concept, first historically, because it stated that dendritic cells not only had to capture antigens but also had to differentiate extensively to initiate immunity [21, 22]. At the time, the terms “accessory” and “sensitizing” functions rather than co-stimulation were in use to describe the special roles of dendritic cells beyond antigen processing. Second maturation is really the critical link between innate and many forms of adaptive immunity wherein lym-

phocytes differentiate along many different lines and with important consequences: distinct types of effector cells, long term clonal expansion, and memory. The single term “maturation” clearly cannot specify the many different responses that dendritic cells exhibit when they encounter endogenous (CD40L, thymic stromal lymphopoietin and other cytokines) and exogenous (ligands for Toll-like receptors) stimuli. Nevertheless, I regard “maturation” to be a much better word than “activation” because an intricate and often irreversible process of differentiation takes place [23] rather than a relatively restricted on-off response.

Some of current questions in this central field will be apparent on reading chapters 17–30. First, does the same dendritic cell determine the quality of a lymphocyte response, e.g. tolerance vs. immunity, CD4 vs. CD8 responses, Th1 vs. Th2, or are there distinct dendritic cells that are devoted to the control of these different key outcomes of antigen presentation? Second, how must dendritic cells differentiate to become potent stimulators of Th1 type CD4 responses and CD8 killer responses? It has been believed for some time that this required signal one (MHC peptide) and signal two (B7 co-stimulators), but recent evidence shows that additional differentiation mediated via CD40 is required, even after dendritic cells are successfully presenting MHC peptide complexes and expressing high levels of co-stimulatory molecules, both membrane bound and cytokines [24]. These observations were made with NKT lymphocytes as inducers of dendritic cell maturation, but the same may well be true for microbial stimuli. Third, what types of dendritic cell products are needed for different types of responses? With respect to the key Th1 vs. Th2 decision, new players other than IL-12 need to be considered, e.g. the recent report that dendritic cells use delta and jagged Notch ligands to elicit Th1 and Th2 responses respectively [25]. A long neglected topic is the importance of dendritic cells in memory. Dendritic cells can induce memory, but how? Fifth, how do dendritic cells select the type of lymphocyte that they will interact with? Are all maturing dendritic cells able to interact with NK, NKT, T and B cells, or does the maturation stimulus and dendritic cell subset govern the outcome? This a long list of unknowns, but they pertain to issues of broad impact in immunology.

1.3

Dendritic Cells in Disease Pathogenesis

1.3.1

Chapters 31–51, Dendritic Cells in Infectious and Other Diseases

The interface of microbiology with immunology has been energized by the discovery that Toll-like receptors mediate recognition of a diverse array of microbial ligands [26, 27], and as one consequence, drive the maturation of dendritic cells [28–30]. Many other central areas of medicine also involve hematopoietic cells and immune responses – transplantation, allergy, autoimmunity, cancer, even it now appears, neurodegeneration and atherosclerosis. Immunology can contribute significantly to these prevalent and enigmatic diseases. Chapters 31–51 provide exam-

ples in which dendritic cells are being investigated to understand the development of disease.

1.3.2

Some Questions on the Roles of Dendritic Cells in Diseases

In transplantation, we need to understand more about the initiation of immunity, i.e. what processes in the graft allow dendritic cells to initiate immunity both by the direct pathway (graft dendritic cells present antigens to host T cells) and indirect pathway (host dendritic cells present antigens from the graft)? In allergy, there are real mysteries on how dendritic cells polarize to Th2, particularly in the lung, where this seems to be a Th2 prone environment. There is exciting data that thymic stromal lymphopoietin made by epithelial cells condition a subset of myeloid dendritic cells to induce “inflammatory Th2 cells” (T cells that make not only IL-4 but also TNF α instead of IL-10) [31]. In autoimmunity, particularly lupus, blood monocytes are differentiating along a dendritic cell pathway [32], and this may lead to immunity to self antigens, particularly complexes of autoantigens and antibody [33, 34]. Dendritic cells may be part of a circuit that allows a basic defect in autoantibody formation [35] to bring about autoimmunity. Immune complexes can trigger conventional [33] and plasmacytoid dendritic cells [34] to produce type I interferon, and these interferons may also help expand autoreactive T cells, which in turn increase the switching and affinity of autoreactive B cells. Likewise, the hygiene hypothesis may transpire via dendritic cells. Exposure to microbial stimuli leads to dendritic cell maturation, and the maturing cells are able to induce different types of regulatory and suppressor cells that suppress allergy and autoimmunity [36–38]. Can the immune system be energized against cancer by dampening the mechanisms used by tumors to suppress dendritic cell function, especially maturation [39]? And as the chapters will discuss, many examples of chronic infection are now being analyzed at the levels of dendritic cells. HIV remains the most urgent, since the virus may co-opt dendritic cells to enhance replication in T cells, to induce regulatory cells, and to block maturation [40]. This area of research is limited by the many demands of doing human studies [41]. It will be important for the scientific community to have the conviction to overcome these obstacles, since significant and challenging scientific issues need to be addressed.

1.4

Dendritic Cells and the Design of Vaccines and New Therapies

1.4.1

Chapters 52–55, Dendritic Cells in Immunotherapy

It is not simply a matter of “applied science” to identify new preventions and therapies. Rather the identification of new cures and treatments provide challenging questions for research. The final chapters consider some of these issues. How can

tumor antigens be delivered to dendritic cells, and what maturation stimuli are best to use, especially *ex vivo* where dendritic cells are potentially exciting adjuvants for active immunization [42, 43]? Can dendritic cells be mobilized to bring about therapeutic immunity? Does the newly recognized capacity of dendritic cells to induce suppressor T cells interfere with immune therapy, but on the other hand, provide new ways to treat autoimmunity and allergy and transplant rejection? Again, the stage is set for immunology to contribute to the design of new preventions and therapies, and dendritic cell biology will be an important part of these initiatives.

1.4.2

Dendritic Cells and the Design of Vaccines against Infectious Diseases

One area that is not yet well developed, and therefore not addressed extensively by this book, is that of the immunological approach to vaccines against global infectious diseases. The international effort remains exclusively directed to microbial approaches and microbial vectors. It is perplexing that immunology has not been able to contribute more to the urgent need for new vaccines, but I think this will change. With the need for more effective vaccines, particularly in infections like HIV, malaria and tuberculosis – where cell mediated immunity is likely to be critical – segments of the scientific community are coming to understand that one cannot simply ordain that this or that strategy is “immunogenic” without trying to understand the basis for vaccine efficacy or inefficacy and the correlates of protection. Nevertheless, the field still views vaccines in a bipartite manner, vaccines plus lymphocytes, whereas there is a critical third party or intermediary, dendritic cells.

Many obstacles, imposed by the pathogen, need to be considered in developing vaccines against HIV, TB, malaria and others. However, I believe that the central current obstacle is the need for research to learn to elicit strong immunity and memory in patients, especially T-cell mediated immunity. The many adjuvant roles of dendritic cells, if harnessed, could prove fruitful [44]. It is hoped that some of the increasing resources that are now being directed to vaccine design will bring this about. This book portrays a *ménage à trois* – antigens, lymphocytes and dendritic cells – and provides valuable perspectives to overcome the gap in identifying antigen specific vaccines and therapies.

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